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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/857,995	10/05/2001	John P. McKearn	CU-2560 RJS	4037

7590 11/25/2002

Mr. James M. Warner
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EXAMINER
PATEL, SUDHAKER B

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 11/25/2002

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/857,995	John P.Mckearn et al
Examiner	**Art Unit**
Sudhaker Patel	1624

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Oct 24, 2002

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-3, 11, 21, 43-46, 54, 71, 86, 87, and 107-109 is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-3, 11, 21, 43-46, 54, 71, 86, 87, and 107-109 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☒ Interview Summary (PTO-413) Paper No(s). 17
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' communication paper # 16 dated 10/24/02 is acknowledged. The claims in this application are the claims 1-3,11,21,43-46, 54, 71,86-87, 107-109.

Applicants arguments and remarks have been considered, but not found persuasive for the allowance of the case at this stage for the reasons already stated in earlier office action paper #14 dated 7/17/02, and the bellow mentioned additional reasons:

Examiner's position is as follows:

I. Restriction/election: Applicants have elected invention of Group I, claims 1-3,11,21,43-46, 54, 71,86-87, 107-109 drawn to simple compositions, a method of use, and a method of making composition wherein MMP inhibitor is compound # 11, and Irinotecan or Topotecan together with radiation for treatment of neoplasia disorder in a mammal.

The restriction/election is deemed to be proper, and is now made FINAL.

II. Rejections under 35 USC 112 paragraph one: Applicants' arguments and remarks have been considered but not found persuasive for the reasons already stated in previous office action paper # 14 dated 7/17/02.

Applicants' reliance on the Brana decision is erroneous since the facts were different in more than one respect from the instant case. Compounds on appeal were of a much narrower scope and there were no method claims. Said compounds were similar in structure to compounds displaying in vivo anti-tumor activity based on art-recognized in vivo tests and also tested favorably in an in vivo test. Thus contrary to Brana it is not evident that at the time of applicants'

effective filing date(12/23/1998) that MMP inhibitors having such a diversity of susbtituents onThiomorpholine molecule together with irinotecan or topotecan were well known for preventing neoplasia or other uses urged treatable by combination therapy either alone or with radiation based simply on assay testing relied on herein.

Claims 1,28,43,44,71,86,107,108 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for the specific neoplasia disorder and type of treatment disclosed, does not reasonably provide enablement for the terms "neoplasia disorder" and preventing the in a mammal". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to and use the invention commensurate in scope with these claims. The terms "neoplasia disorder" in claims 1,44,107,108 preventing in mammal" in claims lack clear exemplary support in the specification as filed. Specification on page 171 line recites "dosing of MMPI and antineoplastic agent" but fails to define the mode of administration. The Carter et al reference is cited to show that cisplatin is "inactive orally"(page 107, line 23). The specification remains silent about the mode of administration for MMPI(AG 3340) in combination with irinotecan or topotecan for disorders related to neoplasia and lung(see page 173), and Example 1 for lung cancer (see page 178, lines 5-31, and pages 183-184).

Current status of combinational chemotherapy:

Tumolo et al (PubMed Abstract:11742701, also cited as Lung Cancer 2001 December ;34 Suppl.. 4 pages 37-46) states that several drugs (also alternative to cisplatin) have been used in

combination with TP1-I, but to date the higher remission rate obtained in combination is not translated into a more prolonged survival in comparison with TP1-I alone. On the other hand, the toxicity of TP1-I combinations is greater that those of TP1-I used alone. The superior efficacy of combinations versus TP1-I used alone remains an open question. Furthermore, the best schedule for TP1-I has not been completely elucidated".

Furthermore, the cancer therapy art remains highly unpredictable, and no examples exist for efficacy of the combination against neoplasia disorders generally. Therefore, based on the nature of the invention and lack of guidance and working examples and extreme breadth of the claims, one skilled in this art could not use the entire scope of the claimed invention without induce experimentation. Changing the term "neoplasia disorder" to specific neoplasia disorders and the term "treating" to the specific mode of administration would overcome this rejection.

III. New Rejections:

IIIA. ***Double Patenting***

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 1, 44 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of copending Application No. 09843132 and No. 10150546. Although the conflicting claims are not identical, they are not patentably distinct from each other because: 1). The subject matter is related to combinational treatment of neoplasia and cancer as claimed herein.

2). Both of the applications are claiming priority from Provisional Application 60113786 filed 12/23/98 as claimed herein.

Application Sr. No. 09843132 is with the legal instruments team and Application Sr. No. 10150546 has been dispatched from preexam section but not yet docketed to examiner.

Because these applications are in transit, they are not available for review by the examiner.

There are several other applications claiming Priority from the Provisional Application 60113786, for example US. Application Sr. Nrs.:

09385214; 09470951;09857873;09868063;10135793;10212523, and examiner could not review all of these for the above stated reasons. Applicants are urged to provide necessary information disclosing their relevancy to the instant application as it will be necessary for consideration and review during the prosecution for the same.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Examiner tried to contact the applicants on 11/21/02 to discuss this situation, but the applicants could not be reached(see interview summary).

IIIB. ***Claim Rejections - 35 U.S.C. § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 109 is duplicate of claim 87. Cancellation is required.

IIIC. ***Claim Rejections - 35 U.S.C. § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3,11,21,43-46, 54, 71,86-87, 107-109 are rejected under 35 U.S.C. 103(a) as being unpatentable over Karameris et al(PubMed Abstract: 9412577, also cited as Am. J. Respir. Crit Care Med 1997 December;156(6):1930-6) taken with Bunn et al (PubMed Abstract:8052874, also cited as Semin Oncol 1994 Jun;21(3 Suppl. 6): 49-59).

Karameris states that " Our results suggest that there is a significant association of the expression of MPs and MIs with both the local and metastatic potential and the degree of cellular differentiation of SCLCs, and that this association is clinically important because of its prognostic and therapeutic implications".

The other reference Bunn et al states that" "Many randomized studies have compared radiation therapy alone with radiation plus cisplatin-based chemotherapy in locally advanced, inoperable, stages IIIA and IIIB non-small lung cancer..... However, there are many negative randomized studies evaluating postoperative chemotherapy, especially with non-cisplatin-based regimens, and further studies are obviously needed. Many new agents have produced exciting preliminary results. Responses rated in excess of 20% were reported for paclitaxel, Topotecan, and gemcitabine. Studies in the next few years will help to define the ultimate role of these agents.

Karameris teaches the role of MPs and MIs for their prognostic and therapeutic implications. The other reference teaches the possibitily of using Irinotecan and Topotecan with combined-modality approach.

The references do not teach the two ingredients together. Accordingly, one skilled in this art would find ample motivation from the prior art supra to combine the well known anti-lung cancer drugs together where the results obtained thereby are no more that the additive effects of the ingredients. See In re Sussman 1943 C.D. 518. The specification fails to set forth any data showing and unexpected results for the claimed combinational therapy with or without radiation.

Similar is the conclusion reported in the International Preliminary Examination Report for Application No. PCT/US99/30699 which is related to instant application and cited by the applicants(see Section IV on page 5 and section V on page 5 last paragraph).

The cited report of Section IV states that " The subject matter of the present application is the use of a combination of a MMP inhibitor and an antineoplastic agent selected from a given list for the treatment of tumors and neoplasia, in some claims radiation is additionally used....., the only feature these have in common is that they are antineoplastic agents. It is already known in the prior arts to use the said general combination in the treatment of neoplastic diseases".

The cited report of Section V states that " It is well known in the prior art(s) to use combinations of MMP-inhibitors together with other antineoplastic agents in the treatment of cancer(U.S.P. 5672583; U.S.P. 5629343; WO 9748685). Moreover, anastrozole, irinotecan and topotecan are well known antineoplastic agents(Biological Abstracts, Vol.00, Philadelphia,

PA,USA Abstract No. Prev 199800349798, Barni Sandro et al; Mueller-Bohn T in Deutsche Apotheker Zeitung, 137/41,54-55(1997). It can therefore not be considered as inventive tom use the claimed combinations of a MMP inhibitor with anastrozole, irinotecan or topotecan, especially since to special or unexpected effect has been shown".

IV. *Conclusion*

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker Patel,D.Sc.Tech. whose telephone number is (703) 308-4709. The examiner can normally be reached on Monday thru' Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by the phone are unsuccessful, the examiner's supervisor, Dr.Mukund Shah can be reached at (703) 308 4716 or Sr. Examiner Mr. Richard Raymond at(703) 308 4523.

A facsimile center has been established for Group 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4556 or (703) 305-3592.

Any inquiry of general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 1235.

JOHN M. FORD
PRIMARY EXAMINER
GROUP 1624

SP/11/24/02

MUKUND SHAH

SUPERVISORY PATENT EXAMINER

ART UNIT 1624